Claims 1-19 are pending in this application.

The terminal disclaimer filed on 10/3/2008 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent 7,164,005 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Applicants' election of the invention of Group I (the biologically active labile agent is exendin-4) in the response filed on 7/14/2008 is acknowledged. Applicant further elected the following single disclosed species:

(1) poly(lactide-co-glycolides) as the biocompatible polymer; and

(2) triamcinolone compounds as the corticosteroid.

Applicants do not traverse these elections. Because applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicants do however traverse the election of triamcinolone acetonide as a single specific corticosteroid compound. Applicants' remarks are noted and the election of species requirement to the extent that it required election of a single specific triamcinolone compound is hereby withdrawn.

Claims 16-19 are withdrawn from further consideration as being directed to non-elected subject matter. Claims 1-15 will presently be examined to the extent that they read on the elected subject matter of record.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 depends on claim 4. Claim 5 requires the second biocompatible polymer to be different from the first biocompatible polymer but claim 4 requires the two biocompatible polymers to be the same. This is unclear and indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Interpretation of the claimed invention

The claimed invention under examination here is directed to a method for sustained in vivo release of **exendin-4** for a period of at least two weeks. Exendin-4 is a **hypoglycemic** agent, which is useful as an anti-diabetic agent.

The claims require administering exendin-4 with a **corticosteroid (hyperglycemic agent)**, wherein the corticosteroid is "in an amount sufficient to modify the release profile of [exendin-4]" and "provide increased bioavailability of the [exendin-4]." The specification does not disclose exactly what this amount is other than in one example involving exendin-4. In example 10 (specification pages 58-61), Sprague-Dawley rats were administered 120 mg of 1% exendin + 10 mg of 2% triamcinolone and 40 mg of 3% exendin + 10 mg of 2% triamcinolone.[1] This calculates to an exendin-4 to triamcinolone ratio of 6:1 for both combinations.

Most of the claims are open to any corticosteroid. Dependent claim 7 recites a long list of corticosteroids. Claim 8 is limited to triamcinolone compounds.

Actual reduction to practice and thus written description met in part

The above noted example of 120 mg of 1% exendin + 10 mg of 2% triamcinolone and 40 mg of 3% exendin + 10 mg of 2% triamcinolone in the tested formulations meet the written description requirement of 35 USC 112, first paragraph **for non-diabetic subjects.**

Analysis of remaining subject matter

While exendin-4 is a specifically claimed active agent and corticosteroids (well known) are recited with dependent species claims, **their exact amounts and ratios are not set forth in the claims**. Besides the single example of exendin-4 + triamcinolone discussed above for non-diabetic subjects, there is no other disclosure as to how much exendin-4 and corticosteriod are to be present in the sustained release composition and delivered to the subject, diabetic subject in particular, for a release period of at least two weeks. In other words, there is no further written description as to what exactly is "an amount sufficient to modify the release profile of [exendin-4]" and an amount to “provide increased bioavailability of the [exendin-4]” for subjects in general and diabetic subjects in particular.

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[1] See also specification page 25, lines 19-24.

Exendin-4 is an antidiabetic agent with hypoglycemic activity. Thus, the subject receiving the claimed invention treatment includes diabetic patients.

However, corticosteroids are generally contraindicated for diabetic patients because they induce glucose intolerance and insulin resistance. See for example HCAPLUS abstract 1994:622315 (cited in the previous Office action) and Medline abstract 2000463624. Willi et al. disclose that glucocorticosteroids[2] “induce insulin resistance in humans and **can cause diabetes or aggravate pre-existing diabetes**” (page 88, left column, first paragraph) (emphases added). Schacke et al. similarly disclose that glucocorticosteroids are “**associated with the risk of hyperglycemia in patients without known diabetes mellitus (induction of diabetes) and worsened glycemic control in diabetic patients (aggravation of diabetes)**.” (page 33, left column, last paragraph) (emphases added).

Therefore, there is substantial unpredictability as to delivering an antidiabetic agent with hypoglycemic activity (exendin-4) with an hyperglycemic agent (corticosteroid) to a subject such as a diabetic patient in need of an hypoglycemic agent and not a hyperglycemic agent, let alone providing increased bioavailability of exendin-4 and modifying the release profile of the exendin-4 for a period of at least two weeks. The two agents have the opposite effects, and there is no known or disclosed correlation between corticosteroids and the functionality of this class of compounds to provide the claimed release profile and increased bioavailability in conjunction with exendin-4, as claimed. Consequently, without sufficient explicit disclosure as to specific formulation and dosage amounts and ratios of exendin-4 and corticosteroids, one skilled in the art would not have recognized the applicants to be in possession of the claimed invention as broadly claimed herein.

For these reasons, the claims fail to meet the written description requirement of 35 USC 112, first paragraph.

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administration of exendin-4 + corticosteroids to **non-diabetic subjects**, does not reasonably provide enablement for administration of the same to diabetic subjects, including diabetic humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

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[2] Glucocorticosteroids include many of the corticosteroids recited by applicant in the instant claims, including betamethasone, dexamethasone, flucortolone, hydrocortisone, methylprednisolone, prednisolone, triamcinolone.

The claimed invention under examination here is directed to a method for sustained in vivo release of **exendin-4** for a period of at least two weeks. Exendin-4 is a **hypoglycemic** agent, which is useful as an anti-diabetic agent.

The claims require administering exendin-4 with a **corticosteroid (hyperglycemic agent)**, wherein the corticosteroid is "in an amount sufficient to modify the release profile of [exendin-4]" and “provide increased bioavailability of the [exendin-4].” The specification does not disclose exactly what this amount is other than in one example involving exendin-4. In example 10 (specification pages 58-61), disclosed are 120 mg of 1% exendin + 10 mg of 2% triamcinolone and 40 mg of 3% exendin + 10 mg of 2% triamcinolone[3] administered to Sprague-Dawley rats. This calculates to an exendin-4 to triamcinolone ratio of 6:1 for both combinations.

Most of the claims are open to any corticosteroid. Dependent claim 7 recites a long list of corticosteroids. Claim 8 is limited to triamcinolone compounds.

Exendin-4 is an antidiabetic agent with hypoglycemic activity. Thus, the subject receiving the claimed invention treatment includes diabetic patients.

However, corticosteroids are generally contraindicated for diabetic patients because they induce glucose intolerance and insulin resistance. See for example HCAPLUS abstract 1994:622315 (cited in the previous Office action) and Medline abstract 2000463624. Willi et al. disclose that glucocorticosteroids[4] “induce insulin resistance in humans and **can cause diabetes or aggravate pre-existing diabetes**" (page 88, left column, first paragraph) (emphases added). Schacke et al. similarly disclose that glucocorticosteroids are "**associated with the risk of hyperglycemia in patients without known diabetes mellitus (induction of diabetes) and worsened glycemic control in diabetic patients (aggravation of diabetes)**." (page 33, left column, last paragraph) (emphases added).

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[3] See also specification page 25, lines 19-24.

[4] Glucocorticosteroids include many of the corticosteroids recited by applicant in the instant claims, including betamethasone, dexamethasone, flucortolone, hydrocortisone, methylprednisolone, prednisolone, triamcinolone.

Therefore, there is substantial unpredictability as to delivering an antidiabetic agent with hypoglycemic activity (exendin-4) with a hyperglycemic agent (corticosteroid) to a subject such as a diabetic patient, let alone providing increased bioavailability of exendin-4 and modifying the release profile of the exendin-4 for a period of at least two weeks. The two agents have the opposite effects, and there is no known or disclosed correlation between corticosteroids and the functionality of this class of compounds to provide the claimed release profile and increased bioavailability in conjunction with exendin-4, as claimed. At a minimum it would have been unpredictable to the skilled person in this art how and what amount/ratio of a hyperglycemic agent would increase bioavailability of a hypoglycemic agent, exendin-4, for a sustained period of at least two weeks in a diabetic subject. Further, it would have been unpredictable as to whether any amount or ratio for one corticosteroid would be indicative of suitable amount and ratio for a different corticosteroid.

The level of the ordinary skill in this art is high, because treatment of diabetes with drugs requires a medical degree and license.

The amount of direction provided by the inventors has been discussed above, and to reiterate, it is insufficient. There is no specific disclosure as to the amount and ratio of corticosteroid to use in conjunction with exendin-4 (the only disclosure is in the same functional language as discussed above). There is only one example given for exendin-4 + triamcinolone, and that example did not use diabetic subjects and thus does not show the claimed effects (release profile modification and bioavailability increase) in diabetic subjects. This is critical because especially in a diabetic patient, the “bioavailability” of the hypoglycemic exendin-4 would be negatively impacted by the hyperglycemic corticosteroids.

Weighing all these factors, it can be determined that one skilled in the art would be faced with a quantity of experimentation that would be undue to make and use the invention as claimed.

Applicants’ copending 11/826,694 is noted. Two claims are currently pending, and the claims **do not specifically recite exendin-4**, although corticosteroid + “peptide” is claimed for modifying release profile and increasing bioavailability of the peptide. However, the specification explicitly discloses exendin-4 as a suitable peptide in this invention (paragraph bridging pages 14 and 15). Therefore, the claims in this copending application must be interpreted to encompass exendin-4.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 12, 14-15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 11/826,694. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons.

Claim 1 of copending application is directed to a method comprising administering a sustained release composition comprising a poly(lactide-co-glycolide) polymer having a peptide and a corticosteroid incorporated therein to a subject, wherein the corticosteroid is present in an amount sufficient to modify the release profile of the peptide from the polymer and provide increased bioavailability of the peptide.

Although exendin-4 is not explicitly recited in the copending claim, it is encompassed by the claim (see the discussion on the previous page of this Office action). Therefore, one having ordinary skill in the art would have recognized the instant claimed invention, to the extent that it is enabled, as an obvious variation of the invention set forth in claim 1 of 11/826,694.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

For these reasons, all claims must be rejected. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to JOHN PAK whose telephone number is **(571)272-0620.** The Examiner can normally be reached on Monday to Friday from 8 AM to 4:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's SPE, Johann Richter, can be reached on **(571)272-0646**.

The fax phone number for the organization where this application or proceeding is assigned is **(571)273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

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/John Pak/
Primary Examiner, Art Unit 1616